



**Attachment II**

**Irinotecan Hydrochloride Injection, 20 mg/mL**

**Draft Labeling Proposed by Mayne Pharma (USA) Inc.**

## IRINOTECAN HYDROCHLORIDE INJECTION

**R<sub>x</sub>** only

### For Intravenous Use Only

#### WARNINGS

Irinotecan Hydrochloride Injection should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Irinotecan Hydrochloride Injection can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or shortly after infusion of Irinotecan Hydrochloride Injection) may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by atropine (see **PRECAUTIONS, General**). Late diarrhea (generally occurring more than 24 hours after administration of Irinotecan Hydrochloride Injection) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide. Patients with diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated or antibiotic therapy if they develop ileus, fever, or severe neutropenia (see **WARNINGS**). Administration of Irinotecan Hydrochloride Injection should be interrupted and subsequent doses reduced if severe diarrhea occurs (see **DOSAGE AND ADMINISTRATION**).

Severe myelosuppression may occur (see **WARNINGS**).

#### DESCRIPTION

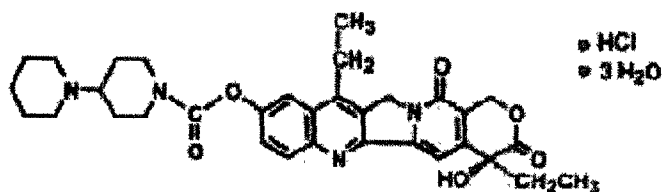
Irinotecan Hydrochloride Injection is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11.

Irinotecan Hydrochloride Injection is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in three single-dose sizes: 2 mL-fill vials contain 40 mg irinotecan hydrochloride, 5 mL-fill vials contain 100 mg irinotecan hydrochloride and 25 mL-fill vials contain 500 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan Hydrochloride Injection is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. The chemical name is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride,

trihydrate.

Its structural formula is as follows:



### **Irinotecan Hydrochloride**

Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula  $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$  and a molecular weight of 677.19. It is slightly soluble in water and organic solvents.

### **CLINICAL PHARMACOLOGY**

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan (see **Pharmacokinetics**). The precise contribution of SN-38 to the activity of Irinotecan Hydrochloride Injection is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

### **Pharmacokinetics**

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms

are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m<sup>2</sup>, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m<sup>2</sup> determined in two clinical studies in patients with solid tumors are summarized in Table 1:

**Table 1. Summary of Mean (±Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors**

Dose (mg/m <sup>2</sup> )	Irinotecan					SN-38		
	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng·h/mL)	t <sub>1/2</sub> (h)	V <sub>z</sub> (L/m <sup>2</sup> )	CL (L/h/m <sup>2</sup> )	C <sub>max</sub> (ng/mL)	AUC <sub>0-24</sub> (ng·h/mL)	t <sub>1/2</sub> (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8 <sup>a</sup> ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4 <sup>a</sup> ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7 <sup>b</sup> ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0 <sup>b</sup> ±4.3

C<sub>max</sub> - Maximum plasma concentration

AUC<sub>0-24</sub> - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion

t<sub>1/2</sub> - Terminal elimination half-life

V<sub>z</sub> - Volume of distribution of terminal elimination phase

CL - Total systemic clearance

<sup>a</sup> Plasma specimens collected for 24 hours following the end of the 90-minute infusion.

<sup>b</sup> Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

**Metabolism and Excretion:** The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1\*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1\*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients who were homozygous for UGT1A1\*28 had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m<sup>2</sup>) to 50% (300 mg/m<sup>2</sup>).

### **Pharmacokinetics in Special Populations**

**Geriatric:** In studies using the weekly schedule, the terminal half-life of irinotecan was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized AUC<sub>0-24</sub> for SN-38 in patients who were at least 65 years of age was 11% higher than in patients younger than 65 years. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan. The pharmacokinetics of irinotecan given once every 3 weeks has not been studied in the geriatric population; a lower starting dose is recommended in patients 70 years or older based on clinical toxicity experience with this schedule (see **DOSAGE AND ADMINISTRATION**).

**Pediatric:** See **Pediatric Use** under **PRECAUTIONS**.

**Gender:** The pharmacokinetics of irinotecan do not appear to be influenced by gender.

**Race:** The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

**Hepatic Insufficiency:** Irinotecan clearance is diminished in patients with hepatic dysfunction while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. However, the tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made. See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS: Patients at Particular Risk** Sections.

**Renal Insufficiency:** The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated.

### **Drug-Drug Interactions**

**Anticonvulsants:** Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or carbamazepine. The appropriate starting dose for patients taking these anticonvulsants has not been formally defined. The following drugs are also CYP3A4 inducers: rifampin, rifabutin. For patients requiring anticonvulsant treatment, consideration should be given to substituting non-enzyme inducing anticonvulsants at least 2 weeks prior to initiation of irinotecan therapy.

Dexamethasone does not appear to alter the pharmacokinetics of irinotecan.

**St. John's Wort:** St. John's Wort is an inducer of CYP3A4 enzymes. Exposure to the active metabolite SN-38 is reduced in patients receiving concomitant St.

John's Wort. St. John's Wort should be discontinued at least 2 weeks prior to the first cycle of irinotecan, and St. John's Wort is contraindicated during irinotecan therapy.

**Ketoconazole:** Ketoconazole is a strong inhibitor of CYP3A4 enzymes. Patients receiving concomitant ketoconazole have increased exposure to irinotecan and its active metabolite SN-38. Patients should discontinue ketoconazole at least 1 week prior to starting irinotecan therapy and ketoconazole is contraindicated during irinotecan therapy.

## CLINICAL STUDIES

### Second-Line Treatment for Recurrent or Progressive Metastatic Colorectal Cancer After 5-FU-Based Treatment

#### Weekly Dosage Schedule

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of Irinotecan Hydrochloride Injection in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on actual clinical benefit, such as effects on survival and disease-related symptoms. In each study, Irinotecan Hydrochloride Injection was administered in repeated 6-week cycles consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of Irinotecan Hydrochloride Injection in these trials were 100, 125, or 150 mg/m<sup>2</sup>, but the 150-mg/m<sup>2</sup> dose was poorly tolerated (due to unacceptably high rates of grade 4 late diarrhea and febrile neutropenia). Study 1 enrolled 48 patients and was conducted by a single investigator at several regional hospitals. Study 2 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 2 received a starting dose of 125 mg/m<sup>2</sup>. Study 3 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m<sup>2</sup> but was reduced to 100 mg/m<sup>2</sup> because the toxicity seen at the 125-mg/m<sup>2</sup> dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. The results of the individual studies are shown in Table 2.

Table 2. Weekly Dosage Schedule: Study Results

	Study			
	1	2	3	
Number of Patients	48	90	64	102
Starting Dose (mg/m <sup>2</sup> /wk x 4)	125 <sup>a</sup>	125	125	100
<b>Demographics and Treatment Administration</b>				
Female/Male (%)	46/54	36/64	50/50	51/49
Median Age in years (range)	63 (29-78)	63 (32-81)	61 (42-84)	64 (25-84)
Ethnic Origin (%)				
White	79	96	81	91
African American	12	4	11	5
Hispanic	8	0	8	2
Oriental/Asian	0	0	0	2
Performance Status (%)				
0	60	38	59	44
1	38	48	33	51
2	2	14	8	5
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8

Unknown	0	0	0	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81	66	73	68
≤6 months after Adjuvant	15	7	27	28
> 6 months after Adjuvant	2	16	0	2
Classification Unknown	2	12	0	3
Prior Pelvic/Abdominal Irradiation (%)				
Yes	3	29	0	0
Other	0	9	2	4
None	97	62	98	96
Duration of Treatment with Irinotecan Hydrochloride Injection (median, months)	5	4	4	3
Relative Dose Intensity <sup>b</sup> (median %)	74	67	73	81
<b>Efficacy</b>				
Confirmed Objective Response Rate (%) <sup>c</sup> (95% CI)	21 (9.3 - 32.3)	13 (6.3 - 20.4)	14 (5.5 - 22.6)	9 (3.3 - 14.3)
Time to Response (median, months)	2.6	1.5	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3
1-Year Survival (%)	46	31	45	43

<sup>a</sup> Nine patients received 150 mg/m<sup>2</sup> as a starting dose; two (22.2%) responded to Irinotecan Hydrochloride Injection.

<sup>b</sup> Relative dose intensity for Irinotecan Hydrochloride Injection based on planned dose intensity of 100, 83.3, and 66.7 mg/m<sup>2</sup>/wk corresponding with 150, 125, and 100 mg/m<sup>2</sup> starting doses, respectively.

<sup>c</sup> Confirmed ≥ 4 to 6 weeks after first evidence of objective response.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m<sup>2</sup>. Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m<sup>2</sup>. The majority of responses were observed within the first two cycles of therapy, but responses did occur in later cycles of treatment (one response was observed after the eighth cycle). The median response duration for patients beginning therapy at 125 mg/m<sup>2</sup> was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three studies, response rates to Irinotecan Hydrochloride Injection were similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to Irinotecan Hydrochloride Injection had not responded to prior 5-FU. Patients who had received previous irradiation to the pelvis responded to Irinotecan Hydrochloride Injection at approximately the same rate as those who had not previously received irradiation.

#### Once-Every-3-Week Dosage Schedule

**Single-Arm Studies:** Data from an open-label, single-agent, single-arm, multicenter, clinical study involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed following treatment with 5-FU. Patients received a



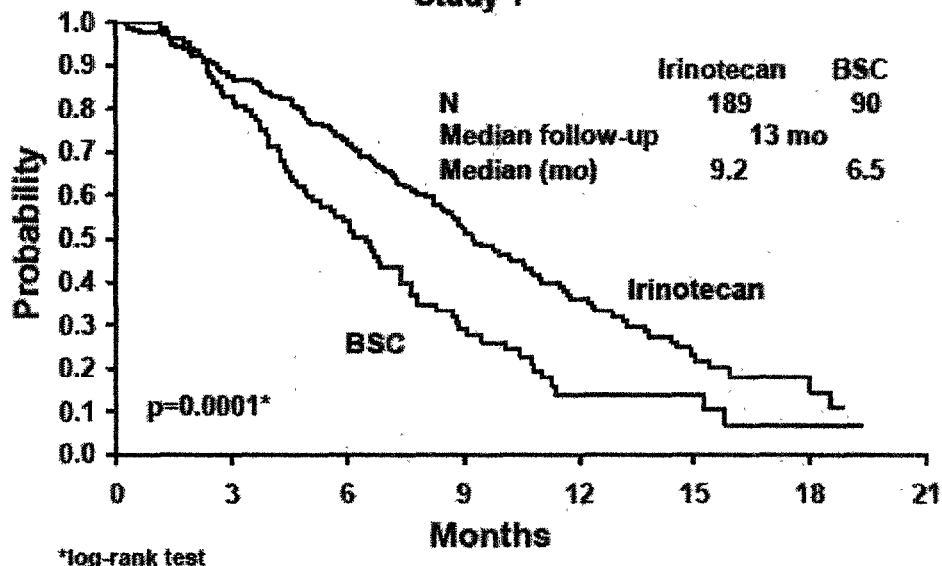
starting dose of 350 mg/m<sup>2</sup> given by 30-minute intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI, 7.0% to 18.1%).

**Randomized Trials:** Two multicenter, randomized, clinical studies further support the use of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In the first study, second-line irinotecan therapy plus best supportive care was compared with best supportive care alone. In the second study, second-line irinotecan therapy was compared with infusional 5-FU-based therapy. In both studies, irinotecan was administered intravenously at a starting dose of 350 mg/m<sup>2</sup> over 90 minutes once every 3 weeks. The starting dose was 300 mg/m<sup>2</sup> for patients who were 70 years and older or who had a performance status of 2. The highest total dose permitted was 700 mg. Dose reductions and/or administration delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Best supportive care was provided to patients in both arms of Study 1 and included antibiotics, analgesics, corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as clinically indicated. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. If late diarrhea persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the second study received one of the following 5-FU regimens: (1) LV, 200 mg/m<sup>2</sup> IV over 2 hours; followed by 5-FU, 400 mg/m<sup>2</sup> IV bolus; followed by 5-FU, 600 mg/m<sup>2</sup> continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m<sup>2</sup>/day protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m<sup>2</sup> IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m<sup>2</sup>/day every week IV for 6 weeks with 2-week rest between cycles. Patients were to be followed every 3 to 6 weeks for 1 year.

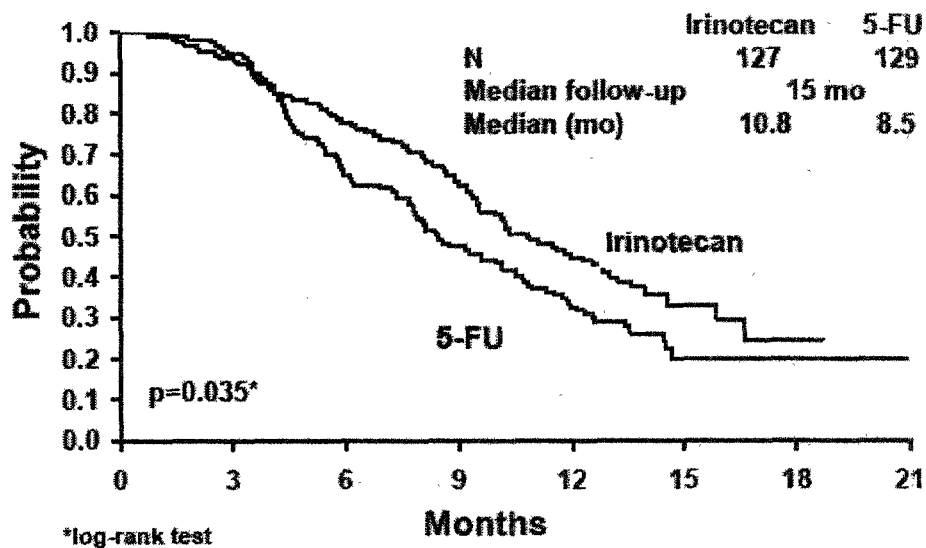
A total of 535 patients were randomized in the two studies at 94 centers. The primary endpoint in both studies was survival. The studies demonstrated a significant overall survival advantage for irinotecan compared with best supportive care ( $p=0.0001$ ) and infusional 5-FU-based therapy ( $p=0.035$ ) as shown in Figures 1 and 2. In Study 1, median survival for patients treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best supportive care. In Study 2, median survival for patients treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy. Multiple regression analyses determined that patients' baseline characteristics also had a significant effect on survival. When adjusted for performance status and other baseline prognostic factors, survival among patients treated with irinotecan remained significantly longer than in the control populations ( $p=0.001$  for Study 1 and  $p=0.017$  for Study 2). Measurements of pain, performance status, and weight loss were collected prospectively in the two studies; however, the plan for the analysis of these data was defined retrospectively. When comparing irinotecan with best supportive care in Study 1, this analysis showed a statistically significant advantage for irinotecan, with longer time to development of pain (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an improvement in performance status

when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive care ( $p=0.002$ ). Because of the inclusion of patients with non-measurable disease, intent-to-treat response rates could not be assessed.

**Figure 1.**  
**Survival Second-Line Irinotecan vs Best Supportive Care (BSC)**  
**Study 1**



**Figure 2.**  
**Survival Second-Line Irinotecan vs Infusional 5-FU**  
**Study 2**



In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of each cycle of therapy, patients completed a questionnaire consisting of 30 questions, such as "Did pain interfere with daily activities?" (1 = Not at All, to 4 = Very Much) and "Do you have any trouble taking a long walk?" (Yes or No). The answers from the 30 questions were converted into 15 subscales, that were scored from 0 to 100, and the global health status subscale that was derived from two questions about the patient's sense of general well being in the past week. In addition to the global health status subscale, there were five functional (i.e., cognitive, emotional, social, physical, role) and nine symptom (i.e., fatigue, appetite loss, pain assessment, insomnia, constipation, dyspnea, nausea/vomiting, financial impact, diarrhea) subscales. The results as summarized in Table 4 are based on patients' worst post-baseline scores. In Study 1, a multivariate analysis and univariate analyses of the individual subscales were performed and corrected for multivariate testing. Patients receiving irinotecan reported significantly better results for the global health status, on two of five functional subscales, and on four of nine symptom subscales. As expected, patients receiving irinotecan noted significantly more diarrhea than those receiving best supportive care. In Study 2, the multivariate analysis on all 15 subscales did not indicate a statistically significant difference between irinotecan and infusional 5-FU.

**Table 3. Once-Every-3-Week Dosage Schedule: Study Results**

	Study 1		Study 2	
	Irinotecan	BSC <sup>a</sup>	Irinotecan	5-FU
Number of Patients	189	90	127	129
<b>Demographics and Treatment Administration</b>				
Female/Male (%)	32/68	42/58	43/57	35/65
Median Age in years (range)	59 (22-75)	62 (34-75)	58 (30-75)	58 (25-75)
Performance Status (%)				
0	47	31	58	54
1	39	46	35	43
2	14	23	8	3
Primary Tumor (%)				
Colon	55	52	57	62
Rectum	45	48	43	38
Prior 5-FU Therapy (%)				
For Metastatic Disease	70	63	58	68
As Adjuvant Treatment	30	37	42	32
Prior Irradiation (%)	26	27	18	20
Duration of Study Treatment (median, months) (Log-rank test)	4.1	--	4.2 (p=0.02)	2.8
Relative Dose Intensity (median %) <sup>b</sup>	94	--	95	81-99
<b>Survival</b>				
Survival (median, months) (Log-rank test)	9.2 (p=0.0001)	6.5	10.8 (p=0.035)	8.5

<sup>a</sup> BSC = best supportive care

<sup>b</sup> Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m<sup>2</sup>/wk corresponding with 350 and 300 mg/m<sup>2</sup> starting doses, respectively.

**Table 4. EORTC QLQ-C30: Mean Worst Post-Baseline Score<sup>a</sup>**

QLQ-C30 Subscale	Study 1			Study 2		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
<b>Global Health Status</b>	47	37	0.03	53	52	0.9
<b>Functional Scales</b>						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0.0003	66	66	0.9
Role	53	35	0.02	54	57	0.9
<b>Symptom Scales</b>						
Fatigue	51	63	0.03	47	46	0.9
Appetite Loss	37	57	0.0007	35	38	0.9
Pain Assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial Impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

<sup>a</sup>For the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

## INDICATIONS AND USAGE

Irinotecan Hydrochloride Injection is indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

## CONTRAINDICATIONS

Irinotecan Hydrochloride Injection is contraindicated in patients with a known hypersensitivity to the drug.

## WARNINGS

### General

Irinotecan Hydrochloride Injection should be used as recommended (see **DOSAGE AND ADMINISTRATION**).

### Diarrhea

Irinotecan Hydrochloride Injection can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of Irinotecan Hydrochloride Injection) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic

symptoms may be prevented or ameliorated by administration of atropine (see **PRECAUTIONS, General**, for dosing recommendations for atropine).

Late diarrhea (generally occurring more than 24 hours after administration of Irinotecan Hydrochloride Injection) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide (see **PRECAUTIONS, Information for Patients**, for dosing recommendations for loperamide). Patients with diarrhea should be carefully monitored, should be given fluid and electrolyte replacement if they become dehydrated, and should be given antibiotic support if they develop ileus, fever, or severe neutropenia. After the first treatment, subsequent weekly chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without need for anti-diarrhea medication. If grade 2, 3, or 4 late diarrhea occurs subsequent doses of Irinotecan Hydrochloride Injection should be decreased within the current cycle (see **DOSAGE AND ADMINISTRATION**).

### **Neutropenia**

Deaths due to sepsis following severe neutropenia have been reported in patients treated with Irinotecan Hydrochloride Injection. Neutropenic complications should be managed promptly with antibiotic support (see **PRECAUTIONS**). Therapy with Irinotecan Hydrochloride Injection should be temporarily omitted during a cycle of therapy if neutropenic fever occurs or if the absolute neutrophil count drops  $<1000/\text{mm}^3$ . After the patient recovers to an absolute neutrophil count  $\geq 1000/\text{mm}^3$ , subsequent doses of Irinotecan Hydrochloride Injection should be reduced depending upon the level of neutropenia observed (see **DOSAGE AND ADMINISTRATION**).

Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing significant neutropenia.

### **Patients with Reduced UGT1A1 Activity**

Individuals who are homozygous for the UGT1A1\*28 allele are at increased risk for neutropenia following initiation of Irinotecan Hydrochloride Injection treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1\*28 allele (see **DOSAGE AND ADMINISTRATION**). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

### **Hypersensitivity**

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed.

### **Colitis/Ileus**

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support (see **PRECAUTIONS**).

### **Renal Impairment/Renal Failure**

Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

### **Thromboembolism**

Thromboembolic events have been observed in patients receiving irinotecan-containing

regimens; the specific cause of these events has not been determined.

### **Pregnancy**

Irinotecan Hydrochloride Injection may cause fetal harm when administered to a pregnant woman. Radioactivity related to  $^{14}\text{C}$ -irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan  $C_{\text{max}}$  and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m<sup>2</sup>). Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan  $C_{\text{max}}$  and AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m<sup>2</sup>) and rabbits (about one-half the recommended human weekly starting dose on a mg/m<sup>2</sup> basis) during the period of organogenesis, is embryotoxic as characterized by increased post-implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan  $C_{\text{max}}$  and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m<sup>2</sup>) and in rabbits at 6.0 mg/kg/day (about one-half the recommended human weekly starting dose on a mg/m<sup>2</sup> basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Irinotecan Hydrochloride Injection.

### **PRECAUTIONS**

#### **General**

**Care of Intravenous Site:** Irinotecan Hydrochloride Injection is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

**Premedication with Antiemetics:** Irinotecan is emetogenic. It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT<sup>3</sup> blocker (e.g., ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of Irinotecan Hydrochloride Injection. Physicians should also consider providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed.

**Treatment of Cholinergic Symptoms:** Prophylactic or therapeutic administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in patients experiencing rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or shortly after infusion of Irinotecan Hydrochloride Injection). These symptoms are expected to occur more frequently with higher irinotecan doses.

**Patients at Particular Risk:** Patients who had previously received pelvic/abdominal radiation and elderly patients with comorbid conditions should be closely monitored.

The use of Irinotecan Hydrochloride Injection in patients with significant hepatic dysfunction has not been established. In clinical trials of either dosing schedule, irinotecan was not administered to patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver metastasis, or transaminase >5 times the upper limit of normal with liver metastasis. In clinical trials of the weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/226];  $p < 0.001$ ). Also see **CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations: Hepatic Insufficiency.** Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with Irinotecan Hydrochloride Injection. Ketoconazole, enzyme-inducing anticonvulsants and St. John's Wort are known to have drug-drug interactions with irinotecan therapy. (See **Drug-Drug Interactions** sub-section under **CLINICAL PHARMACOLOGY**).

### **Information for Patients**

Patients and patients' caregivers should be informed of the expected toxic effects of Irinotecan Hydrochloride Injection, particularly of its gastrointestinal complications, such as nausea, vomiting, abdominal cramping, diarrhea, and infection. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of Irinotecan Hydrochloride Injection) at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Premedication with loperamide is not recommended. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use. Patients should be instructed to contact their physician or nurse if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or evidence of infection.

Patients should be alerted to the possibility of alopecia.

### **Laboratory Tests**

Careful monitoring of the white blood cell count with differential, hemoglobin, and platelet count is recommended before each dose of Irinotecan Hydrochloride Injection.

## **Drug Interactions**

The adverse effects of Irinotecan Hydrochloride Injection, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having similar adverse effects.

Patients who have previously received pelvic/ abdominal irradiation are at increased risk of severe myelosuppression following the administration of Irinotecan Hydrochloride Injection. The concurrent administration of Irinotecan Hydrochloride Injection with irradiation has not been adequately studied and is not recommended.

Lymphocytopenia has been reported in patients receiving Irinotecan Hydrochloride Injection, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

Hyperglycemia has also been reported in patients receiving Irinotecan Hydrochloride Injection. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of Irinotecan Hydrochloride Injection. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.

The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as Irinotecan Hydrochloride Injection than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.

It would be expected that laxative use during therapy with Irinotecan Hydrochloride Injection would worsen the incidence or severity of diarrhea, but this has not been studied.

In view of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by Irinotecan Hydrochloride Injection, the physician may wish to withhold diuretics during dosing with Irinotecan Hydrochloride Injection and, certainly, during periods of active vomiting or diarrhea.

## **Drug-Laboratory Test Interactions**

There are no known interactions between Irinotecan Hydrochloride Injection and laboratory tests.

## **Carcinogenesis, Mutagenesis & Impairment of Fertility**

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan  $C_{max}$  and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m<sup>2</sup> weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Neither irinotecan nor SN-38 was mutagenic in the *in vitro* Ames assay. Irinotecan was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice). No significant adverse effects on fertility and general



reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan  $C_{max}$  and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m<sup>2</sup> weekly) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan  $C_{max}$  and AUC about one-half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m<sup>2</sup> weekly).

### **Pregnancy**

Pregnancy Category D—see **WARNINGS**.

### **Nursing Mothers**

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving therapy with Irinotecan Hydrochloride Injection.

### **Pediatric Use**

The effectiveness of irinotecan in pediatric patients has not been established. Results from two open-label, single arm studies were evaluated. One hundred and seventy children with refractory solid tumors were enrolled in one phase 2 trial in which 50 mg/m<sup>2</sup> of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3-4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3-4 diarrhea was observed in 35 (20.6%) patients. This adverse event profile was comparable to that observed in adults. In the second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m<sup>2</sup> of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the high rate (28.6%) of progressive disease and the early deaths (14%). The adverse event profile was different in this study from that observed in adults; the most significant grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship). Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor trials at dose levels of 50 mg/m<sup>2</sup> (60-min infusion, n=48) and 125 mg/m<sup>2</sup> (90-min infusion, n=6). Irinotecan clearance (mean  $\pm$  S.D.) was  $17.3 \pm 6.7$  L/h/m<sup>2</sup> for the 50mg/m<sup>2</sup> dose and  $16.2 \pm 4.6$  L/h/m<sup>2</sup> for the 125 mg/m<sup>2</sup> dose, which is comparable to that in adults. Dose-normalized SN-38 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x 2 weeks every 3 weeks].

### **Geriatric Use**

Patients greater than 65 years of age should be closely monitored because of a greater risk of late diarrhea in this population (see **CLINICAL PHARMACOLOGY**,

**Pharmacokinetics in Special Populations and ADVERSE REACTIONS, Overview of Adverse Events).** The starting dose of Irinotecan Hydrochloride Injection in patients 70 years and older for the once-every-3-week-dosage schedule should be 300 mg/m<sup>2</sup> (see **DOSAGE AND ADMINISTRATION**).

## **ADVERSE REACTIONS**

### **Second-Line Single-Agent Therapy**

#### **Weekly Dosage Schedule**

In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with Irinotecan Hydrochloride Injection. Seventeen of the patients died within 30 days of the administration of Irinotecan Hydrochloride Injection; in five cases (1.6%, 5/304), the deaths were potentially drug-related. These five patients experienced a constellation of medical events that included known effects of Irinotecan Hydrochloride Injection. One of these patients died of neutropenic sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients recovered with supportive care.

One hundred nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times because of adverse events; 81 (26.6%) patients were hospitalized for events judged to be related to administration of Irinotecan Hydrochloride Injection. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting (18.4%); neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or vomiting (4.9%).

Adjustments in the dose of Irinotecan Hydrochloride Injection were made during the cycle of treatment and for subsequent cycles based on individual patient tolerance. The first dose of at least one cycle of Irinotecan Hydrochloride Injection was reduced for 67% of patients who began the studies at the 125-mg/m<sup>2</sup> starting dose. Within-cycle dose reductions were required for 32% of the cycles initiated at the 125-mg/m<sup>2</sup> dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with Irinotecan Hydrochloride Injection because of adverse events. The adverse events in Table 5 are based on the experience of the 304 patients enrolled in the three studies described in the **CLINICAL STUDIES, Studies Evaluating the Weekly Dosage Schedule**, section.

**Table 5. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum<sup>a</sup>**

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
<b>GASTROINTESTINAL</b>		
Diarrhea (late) <sup>b</sup>	88	
7-9 stools/day (grade 3)	-	31
≥10 stools/day (grade 4)	-	(16)
Nausea	86	(14)
Vomiting	67	17
Anorexia	55	12
Diarrhea (early) <sup>c</sup>	51	6
Constipation	30	8
Flatulence	12	2
Stomatitis	12	0
	10	1

Dyspepsia		0
<b>HEMATOLOGIC</b>		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm <sup>3</sup> (grade 3)	-	(15)
<500/mm <sup>3</sup> (grade 4)	-	(12)
<b>BODY AS A WHOLE</b>		
Asthenia	76	12
Abdominal cramping/pain	57	16
Fever	45	1
Pain	24	2
Headache	17	1
Back pain	14	2
Chills	14	0
Minor infection <sup>d</sup>	14	0
Edema	10	1
Abdominal enlargement	10	0
<b>METABOLIC &amp; NUTRITIONAL</b>		
↓Body weight	30	1
Dehydration	15	4
↑Alkaline phosphatase	13	4
↑SGOT	10	1
<b>DERMATOLOGIC</b>		
Alopecia	60	NA <sup>e</sup>
Sweating	16	0
Rash	13	1
<b>RESPIRATORY</b>		
Dyspnea	22	4
↑Coughing	17	0
Rhinitis	16	0
<b>NEUROLOGIC</b>		
Insomnia	19	0
Dizziness	15	0
<b>CARDIOVASCULAR</b>		
Vasodilation (flushing)	11	0

<sup>a</sup> Severity of adverse events based on NCI CTC (version 1.0)

<sup>b</sup> Occurring > 24 hours after administration of Irinotecan Hydrochloride Injection

<sup>c</sup> Occurring ≤24 hours after administration of Irinotecan Hydrochloride Injection

<sup>d</sup> Primarily upper respiratory infections

<sup>e</sup> Not applicable; complete hair loss = NCI grade 2

### Once-Every-3-Week Dosage Schedule

A total of 535 patients with metastatic colorectal cancer whose disease had recurred or progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients treated with irinotecan died within 30 days of treatment. In three cases

(1%, 3/316), the deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

Hospitalizations due to serious adverse events (whether or not related to study treatment) occurred at least once in 60% (188/316) of patients who received irinotecan, 63% (57/90) who received best supportive care, and 39% (50/129) who received 5-FU-based therapy. Eight percent of patients treated with irinotecan and 7% treated with 5-FU-based therapy discontinued treatment due to adverse events.

Of the 316 patients treated with irinotecan, the most clinically significant adverse events (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic symptoms (47%), and neutropenia (30%). Table 6 lists the grade 3 and 4 adverse events reported in the patients enrolled to all treatment arms of the two studies described in the **CLINICAL STUDIES**, Studies Evaluating the Once-Every-3-Week Dosage Schedule, section.

**Table 6. Percent Of Patients Experiencing Grade 3 & 4 Adverse Events  
In Comparative Studies Of Once-Every-3-Week Irinotecan Therapy<sup>a</sup>**

Adverse Event	Study 1		Study 2	
	Irinotecan N=189	BSC <sup>b</sup> N=90	Irinotecan N=127	5-FU N=129
TOTAL Grade 3/4 Adverse Events	79	67	69	54
<b>GASTROINTESTINAL</b>				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
<b>HEMATOLOGIC</b>				
Leukopenia/Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2
<b>Infection</b>				
without grade 3/4 neutropenia	8	3	1	4
with grade 3/4 neutropenia	1	0	2	0
<b>Fever</b>				
without grade 3/4 neutropenia	2	1	2	0
with grade 3/4 neutropenia	2	0	4	2
<b>BODY AS A WHOLE</b>				
Pain	19	22	17	13
Asthenia	15	19	13	12
<b>METABOLIC &amp; NUTRITIONAL</b>				
Hepatic <sup>c</sup>	9	7	9	6
<b>DERMATOLOGIC</b>				
Hand & foot syndrome	0	0	0	5
Cutaneous signs <sup>d</sup>	2	0	1	3
<b>RESPIRATORY<sup>e</sup></b>	10	8	5	7
<b>NEUROLOGIC<sup>f</sup></b>	12	13	9	4
<b>CARDIOVASCULAR<sup>g</sup></b>	9	3	4	2

OTHER <sup>h</sup>	32	28	12	14
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<sup>a</sup> Severity of adverse events based on NCI CTC (version 1.0)

<sup>b</sup> BSC = best supportive care

<sup>c</sup> Hepatic includes events such as ascites and jaundice

<sup>d</sup> Cutaneous signs include events such as rash

<sup>e</sup> Respiratory includes events such as dyspnea and cough

<sup>f</sup> Neurologic includes events such as somnolence

<sup>g</sup> Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction

<sup>h</sup> Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss

## Overview of Adverse Events

**Gastrointestinal:** Nausea, vomiting, and diarrhea are common adverse events following treatment with Irinotecan Hydrochloride Injection and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of Irinotecan Hydrochloride Injection. In the clinical studies testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was 11 days following administration of Irinotecan Hydrochloride Injection. For patients starting treatment at the 125-mg/m<sup>2</sup> weekly dose, the median duration of any grade of late diarrhea was 3 days. Among those patients treated at the 125-mg/m<sup>2</sup> weekly dose who experienced grade 3 or 4 late diarrhea, the median duration of the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late diarrhea was somewhat greater in patients starting treatment at 125 mg/m<sup>2</sup> than in patients given a 100-mg/m<sup>2</sup> weekly starting dose (34% [65/193] versus 23% [24/102]; p=0.08). The frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years than in patients <65 years (40% [53/133] versus 23% [40/171]; p=0.002). In one study of the weekly dosage treatment, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43% [25/58] versus 16% [5/32]; p=0.01), but there were no gender differences in the frequency of grade 3 and 4 late diarrhea in the other two studies of the weekly dosage treatment schedule. Colonic ulceration, sometimes with gastrointestinal bleeding, has been observed in association with administration of Irinotecan Hydrochloride Injection.

**Hematology:** Irinotecan Hydrochloride Injection commonly causes neutropenia, leucopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia is uncommon. When evaluated in the trials of weekly administration, the frequency of grade 3 and 4 neutropenia was significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48% [13/27] versus 24% [67/277]; p=0.04). In these same studies, patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/266]; p<0.001). There were no significant differences in the frequency of grade 3 and 4 neutropenia by age or gender. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 7% of the patients

receiving weekly treatment; blood transfusions were given to 10% of the patients in these trials.

**Body as a Whole:** Asthenia, fever, and abdominal pain are generally the most common events of this type.

**Cholinergic Symptoms:** Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea. If these symptoms occur, they manifest during or shortly after drug infusion. They are thought to be related to the anticholinesterase activity of the irinotecan parent compound and are expected to occur more frequently with higher irinotecan doses.

**Hepatic:** In the clinical studies evaluating the weekly dosage schedule, NCI grade 3 or 4 liver enzyme abnormalities were observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases.

**Dermatologic:** Alopecia has been reported during treatment with Irinotecan Hydrochloride Injection. Rashes have also been reported but did not result in discontinuation of treatment.

**Respiratory:** Severe pulmonary events are infrequent. In the clinical studies evaluating the weekly dosage schedule, NCI grade 3 or 4 dyspnea was reported in 4% of patients. Over half the patients with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea in these patients is unknown.

**Neurologic:** Insomnia and dizziness can occur, but are not usually considered to be directly related to the administration of Irinotecan Hydrochloride Injection. Dizziness may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

**Cardiovascular:** Vasodilation (flushing) may occur during administration of Irinotecan Hydrochloride Injection. Bradycardia may also occur, but has not required intervention. These effects have been attributed to the cholinergic syndrome sometimes observed during or shortly after infusion of Irinotecan Hydrochloride Injection. Thromboembolic events have been observed in patients receiving Irinotecan Hydrochloride Injection; the specific cause of these events has not been determined.

#### **Other Non-U.S. Clinical Trials**

Irinotecan has been studied in over 1,100 patients in Japan. Patients in these studies had a variety of tumor types, including cancer of the colon or rectum, and were treated with several different doses and schedules. In general, the types of toxicities observed were similar to those seen in U.S. trials with Irinotecan Hydrochloride Injection. There is some information from Japanese trials that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease. As a result of these observations, however, clinical studies in the United States have enrolled few patients with

compromised pulmonary function, significant ascites, or pleural effusions.

### Post-Marketing Experience

The following events have been identified during postmarketing use of Irinotecan Hydrochloride Injection in clinical practice. Cases of colitis complicated by ulceration, bleeding, ileus, or infection have been observed. There have been rare cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities (see **WARNINGS**). Rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been observed.

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have also been observed (see **WARNINGS**).

### OVERDOSAGE

In U.S. phase 1 trials, single doses of up to 345 mg/m<sup>2</sup> of irinotecan were administered to patients with various cancers. Single doses of up to 750 mg/m<sup>2</sup> of irinotecan have been given in non-U.S. trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no known antidote for overdosage of Irinotecan Hydrochloride Injection. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

### DOSAGE AND ADMINISTRATION

#### Dosage in Patients with Reduced UGT1A1 Activity

When administered as a single-agent, a reduction in the starting dose by at least one level of Irinotecan Hydrochloride Injection should be considered for patients known to be homozygous for the UGT1A1\*28 allele (See **CLINICAL PHARMACOLOGY** and **WARNINGS**). However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see tables 7-8).

#### Single-Agent Dosage Schedules

##### Dosage Regimens

Irinotecan Hydrochloride Injection should be administered as an intravenous infusion over 90 minutes for both the weekly and once-every-3-week dosage schedules (see **Preparation of Infusion Solution**). Single-agent dosage regimens are shown in Table 7.

Table 7. Single-Agent Regimens of Irinotecan Hydrochloride Injection and Dose Modifications			
Weekly Regimen <sup>a</sup>	125 mg/m <sup>2</sup> IV over 90 min, d 1,8,15,22 then 2-wk rest		
	Starting Dose & Modified Dose Levels <sup>c</sup> (mg/m <sup>2</sup> )		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Once-Every-3-Week Regimen <sup>b</sup>	350 mg/m <sup>2</sup> IV over 90 min, once every 3 wks <sup>c</sup>		
	Starting Dose & Modified Dose Levels (mg/m <sup>2</sup> )		
	Starting Dose	Dose Level -1	Dose Level -2

	350	300	250
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<sup>a</sup>Subsequent doses may be adjusted as high as 150 mg/m<sup>2</sup> or to as low as 50 mg/m<sup>2</sup> in 25 to 50 mg/m<sup>2</sup> decrements depending upon individual patient tolerance.

<sup>b</sup>Subsequent doses may be adjusted as low as 200 mg/m<sup>2</sup> in 50 mg/m<sup>2</sup> decrements depending upon individual patient tolerance.

<sup>c</sup>Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

A reduction in the starting dose by one dose level of Irinotecan Hydrochloride Injection may be considered for patients with any of the following conditions: age ≥65 years, prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients. A reduction in the starting dose by at least one level of Irinotecan Hydrochloride Injection should be considered for patients known to be homozygous for the UGT1A1\*28 allele (See **CLINICAL PHARMACOLOGY** and **WARNINGS**). The appropriate dose reduction in this patient population is not known.

It is recommended that patients receive premedication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. See **PRECAUTIONS, General**.

#### Dose Modifications

Patients should be carefully monitored for toxicity and doses of Irinotecan Hydrochloride Injection should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose-levels described in Table 7, Single-Agent Regimens of Irinotecan Hydrochloride Injection and Dose Modifications, subsequent doses should be adjusted as suggested in Table 8, Recommended Dose Modifications for Single-Agent Schedules. All dose modifications should be based on the worst preceding toxicity.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing this combination therapy. Provided intolerable toxicity does not develop, treatment with additional cycles of Irinotecan Hydrochloride Injection may be continued indefinitely as long as patients continue to experience clinical benefit.

**Table 8. Recommended Dose Modifications For Single-Agent Schedules<sup>a</sup>**

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm<sup>3</sup>, and the platelet count has recovered to ≥100,000/mm<sup>3</sup>, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing Irinotecan Hydrochloride Injection.

Worst Toxicity Grade <sup>b</sup> (Value)	NCI	During a Cycle of Therapy	At the Start of the Next Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle <sup>a</sup>	
			Weekly	Once Every 3 Weeks
No toxicity		Maintain dose level	↑25 mg/m <sup>2</sup> up to a maximum dose of 150 mg/m <sup>2</sup>	Maintain dose level



<b>Neutropenia</b>			
1 (1500 to 1999/mm <sup>3</sup> )	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm <sup>3</sup> )	↓25 mg/m <sup>2</sup>	Maintain dose level	Maintain dose level
3 (500 to 999/mm <sup>3</sup> )	Omit dose until resolved to ≤ grade 2, then ↓25 mg/m <sup>2</sup>	↓25 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>
4 (<500/mm <sup>3</sup> )	Omit dose until resolved to ≤ grade 2, then ↓50 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>
<b>Neutropenic fever</b>	Omit dose until resolved, then ↓50 mg/m <sup>2</sup> when resolved	↓50 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>
<b>Other hematologic toxicities</b>	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
<b>Diarrhea</b>			
1 (2-3 stools/day > pretx <sup>c</sup> )	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	↓25 mg/m <sup>2</sup>	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to ≤ grade 2, then ↓25 mg/m <sup>2</sup>	↓25 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>
4 (≥10 stools/day > pretx)	Omit dose until resolved to ≤ grade 2 then ↓50 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>
<b>Other nonhematologic<sup>d</sup> toxicities</b>			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	↓25 mg/m <sup>2</sup>	↓25 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>
3	Omit dose until resolved to ≤ grade 2, then ↓25 mg/m <sup>2</sup>	↓25 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>
4	Omit dose until resolved to ≤ grade 2, then ↓50 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>	↓50 mg/m <sup>2</sup>

<sup>a</sup> All dose modifications should be based on the worst preceding toxicity

<sup>b</sup> National Cancer Institute Common Toxicity Criteria (version 1.0)

<sup>c</sup> Pretreatment

<sup>d</sup> Excludes alopecia, anorexia, asthenia

## Preparation & Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from Irinotecan Hydrochloride Injection. The use of gloves is recommended. If a solution of Irinotecan Hydrochloride Injection contacts the skin, wash the skin immediately and thoroughly with soap and water. If Irinotecan Hydrochloride Injection contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.<sup>1-7</sup>

## Preparation of Infusion Solution

Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe.

Irinotecan Hydrochloride Injection must be diluted prior to infusion. Irinotecan Hydrochloride Injection should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL. In most clinical trials, Irinotecan Hydrochloride Injection was administered in 250 mL to 500 mL of 5% Dextrose Injection, USP.

The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting.

Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing Irinotecan Hydrochloride Injection and admixtures of Irinotecan Hydrochloride Injection may result in precipitation of the drug and should be avoided. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5%Dextrose Injection, USP, within 24

hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 6 hours if kept at room temperature (15° to 30°C, 59° to 86°F). Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

## HOW SUPPLIED

Each mL of Irinotecan Hydrochloride Injection contains 20 mg irinotecan (on the basis of the trihydrate salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

Irinotecan Hydrochloride Injection is available in single-dose amber glass vials in the following package sizes:

NDC XXXXX-XXX-XX 40 mg/2 mL

NDC XXXXX-XXX-XX 100 mg/5 mL

NDC XXXXX-XXX-XX 500 mg/25 mL

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial should remain in the carton until the time of use.

## REFERENCES

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